



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) **EP 0 756 870 A2**

(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
05.02.1997 Bulletin 1997/06

(51) Int. Cl.⁶: **A61K 31/19**, **A61K 9/08**

(21) Application number: **96111575.5**

(22) Date of filing: **18.07.1996**

(84) Designated Contracting States:
DE ES FR GB GR IT

(72) Inventor: **Dondi, Gilberto**
Cusano Milanino (MI) (IT)

(30) Priority: **03.08.1995 IT MI951720**

(74) Representative: **Klausner, Erich**
c/o Ufficio Internazionale Brevetti
Ing. C. Gregorj S.p.A.
Via Dogana 1
20123 Milano (IT)

(71) Applicant: **Bayer S.p.A.**
20156 Milano (IT)

(54) **Pharmaceutical compositions for topic use on the basis of ketoprofen**

(57) The invention relates to pharmaceutical spray compositions on the basis of ketoprofen, useful for the treatment of rheumatism and traumatic affections.

EP 0 756 870 A2

Description

The topic treatment of rheumatic diseases or traumatic affections is often carried out using topic pharmaceutical formulations such as plasters, ointments, creams, gels, sprays and the like.

5 The aim of the topic treatment is to establish an analgesic and/or therapeutic effect.

The therapeutic effect is established depending on the penetration ability of the drug in the area suffering from the existing pathology.

10 It is generally accepted that the penetration route of a substance inside and through the skin is the skin itself and not other structures such as hair follicles or sudoriferous glands, although these may represent concomitant penetration routes.

There are well-founded reasons to believe that such structures do not constitute the prevalent routes; in humans, for example, palmar or plantar regions are provided with sudoriferous glands in an amount which is three times higher than in the other body regions; however, these regions are less capable of absorbing penetrating substances. Now, therefore, the prevailing opinion among the skilled in the art is that the transport of molecules of pharmacologically 15 active substances occurs through passive diffusion and is strongly affected positively by skin hydration. Ointments which leave an occlusive film on the cutaneous surface produce hydration because of sweat accumulation at the skin-ointment interface and consequently they promote penetration.

Among the other factors affecting the absorbment is heat because it promotes a state of hyperthermia. Cold acts in the opposite way because it slows down the capillary circulation.

20 Among the many preparations available there are two types of spray formulations:

- compositions with a cooling effect which basically favors the analgesic action of the composition
- compositions with a revulsive/rubefacient effect which facilitates the blood supply with a consequent sensation of wellbeing.

25 Recently, attempts have been made to use pharmacologically active substances generally employed parenterally and/or enterally. As a consequence, however, the need arose for agents capable of promoting the drug penetration through the skin.

30 In this connection, a number of different substances have been suggested such as alcohols, polyglycols, surfactants of different structures, without a common or clearly demonstrable result.

The more efficient system in order to assure the effectiveness of the pharmaceutical composition must be based on two types of action:

- a greater blood supply with an increase in skin permeability,
- 35 - a better penetration due to the presence of suitably selected agents.

On the basis of these assumptions, a sprayable pharmaceutical formulation, comprising an antirheumatic/analgesic active substance, such as ketoprofen, was developed, which formulation has the following percent composition (weight/weight):

40

ketoprofen	2-10
isopropyl alcohol	40-80
benzyl nicotinate	0.2-2
45 propylene glycol	5-10
poloxamer	1-10
polyvinylpyrrolidone	2-10
50 ethanolamine	0.9-4.4
water	q.s. to 100

In the above-mentioned formulation, benzyl nicotinate is the rubefacient agent which, as it is known to the skilled in the art, can be substituted with other substances such as, e.g., camphor, menthol, capsicum, or mixtures thereof; propylene glycol and isopropyl alcohol, or other alcohols commonly used in art drugs for topic use, are the principal carriers, poloxamer (ethylene-polyoxypropylene block copolymer), which may be substituted by an equal amount of polyoxyethylated castor oil, acting as a penetration agent, and polyvinylpyrrolidone is added as a film forming agent in order to confer adhesive properties to the skin and to favor the absorption of the topic composition of the present invention.

EP 0 756 870 A2

A critical parameter of the present formulation is the pH value of the ketoprofen solution in the hydroalcoholic carrier in order to give stability to the pharmaceutical composition. The best results were obtained for pH values between 5 and 7. According to the present invention these values can be obtained by adding suitable neutralizing agents such as, e.g., ethanolamine, lysine, triethanolamine, methylglucamine and, generally, any suitable amine of the kind used for the manufacture of pharmaceutical compositions.

The manufacture of ketoprofen spray solutions is carried out by dissolving the ingredients in a previously prepared alcohol-water mixture. Finally, ethanolamine is added and the obtained pH value is checked and adjusted, if necessary.

Then the composition is filled up in glass or pharmacologically inert plastic bottles, such as e.g., opaque, white polyethylene, equipped with a mechanical pump for spraying pharmaceutical compositions for topic use in an exactly dosed amount.

The present invention is better illustrated by the following examples. A person skilled in the art of pharmaceutical compositions will, without any difficulty, be able to adapt the process parameters to the particular needs without, thereby, departing from the gist of the invention.

Example 1

To a solution of:

isopropyl alcohol	69.5 g
purified water	10.0 g
the following ingredients are added under stirring:	
poloxamer 407	2.0 g
menthol	0.2 g
propylene glycol	8.0 g
benzyl nicotinate	0.2 g
polyvinylpyrrolidone 25	4.0 g
ketoprofen	5.0 g

To the so obtained homogenous mixture

ethanolamine	1.1 g
--------------	-------

is added; the final pH value of the preparation is 6.5.

Then the solution is divided and packed in dark glass or white polyethylene bottles, equipped with a mechanical sprayer.

Example 2

To a solution of:

ethyl alcohol	68.9 g
purified water	7.0 g
the following ingredients are added, under stirring:	
poloxamer 407	2.0 g
propylene glycol	10.0 g
benzyl nicotinate	2.0 g
polyvinylpyrrolidone 25	4.0 g
ketoprofen	5.0 g

EP 0 756 870 A2

To the so prepared mixture

ethanolamine	1.1 g
--------------	-------

is added; the final pH value of the preparation is 6.5.

Example 3

To a solution of:

ethyl alcohol	68.9 g
purified water	7.0 g
the following ingredients are added, under stirring:	
polyoxyethylated castor oil	2.0 g
propylene glycol	10.0 g
benzyl nicotinate	2.0 g
polyvinylpyrrolidone 25	4.0 g
ketoprofen	5.0 g

To the so prepared mixture

ethanolamine	1.1 g
--------------	-------

is added; the final pH value of the preparation is 6.5.

Claims

1. A pharmaceutical spray composition, for topic use, on the basis of ketoprofen, characterized in that it has the following percent composition, by weight:

ketoprofen	2 to 10
alcohol	40 to 80
propylene glycol	5 to 10
poloxamer (or polyoxyethylated castor oil)	1 to 10
polyvinylpyrrolidone	2 to 10
ethanolamine	0.9 to 4.4
water	q.s. to 100

2. A pharmaceutical spray composition for topic use, according to claim 1, characterized in that its pH value is in the range of from 5 and 7.

3. A pharmaceutical spray composition for topic use, according to claims 1 and 2, characterized by the following percent composition, in parts by weight:

EP 0 756 870 A2

5

10

15

ketoprofen	5.0
isopropyl alcohol	69.5
purified water	10.0
poloxamer 407	2.0
menthol	0.2
propylene glycol	8.0
benzyl nicotinate	0.2
polyvinylpyrrolidone 25	4.0
ethanolamine	1.1
and a pH value of 6.5.	

20

4. A pharmaceutical spray composition, for topic use, according to claims 1 and 2, characterized by the following percent composition, in parts by weight:

25

30

35

ketoprofen	5.0
ethyl alcohol	68.9
purified water	7.0
poloxamer	2.0
propylene glycol	10.0
benzyl nicotinate	2.0
polyvinylpyrrolidone 25	4.0
ethanolamine	5.0
and a pH value of 6.5.	

40

5. A process for manufacturing a pharmaceutical spray composition, for topic use, on the basis of ketoprofen according to anyone of the preceding claims, characterized in that the ketoprofen is dissolved in a previously prepared alcohol-purified water solution, followed by adding the other components of the composition, under continuous stirring, adjusting the pH to a value in the range of 5 and 7, with a pharmaceutically acceptable amine neutralizing agent.

50

55